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Dietary change as a strategy for preventing cancer

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Abstract

The idea that dietary change can alter risk of malignant disease arose historically from animal experiments and observations of human cancer rates. Diet and cancer hypotheses correspond to one of two conceptual approaches to 'diet': 1) the decomposition approach, focusing on specific nutrients and other chemical constituents of food; and 2) the integrative approach, emphasizing the action of whole foods or food patterns (cuisines). Four types of scientific investigation are available for advancing our understanding of diet and cancer: animal experiments, human metabolic (clinical nutrition) studies, observational epidemiologic studies, and randomized, controlled trials (intervention studies). Each of these study types has its strengths and limitations. Observational epidemiologic studies and trials have the advantage of examining explicit cancer end points in humans. Positive findings from large, randomized dietary intervention studies would be particularly compelling. Results from animal and metabolic research, however, can complement findings from epidemiologic studies and trials. Considerable attention is now being paid to the joint action of dietary factors and 'susceptibility' genes. Finally, the author considers the extent to which dietary change can be considered a realistic strategy for preventing major cancers – those of the lung, breast, prostate, and colorectum.

Dietary change as a strategy for preventing cancer

In their 1981 monograph, *The Causes of Cancer*, Doll and Peto attempted to quantify the proportions of human cancer attributable to various etiologic factors [1]. By focusing on avoidable or modifiable causes of malignant disease, they provided something of a recipe for cancer prevention: if a given percentage of cancer is attributable to exposure to X, then avoidance of exposure to X would result in an equivalent percentage decline in cancer incidence. Among the major etiologic factors identified by Doll and Peto was diet, accounting for an estimated 35% of all human malignancy. The 'confidence interval' around this figure, however, was very wide, 10% to 70%, indicating the substantial scientific uncertainty surrounding whether dietary modification could affect carcinogenesis.

The idea that diet could affect the development of malignant disease emerged from two sources: (1) observations of cancer rates; (2) animal experiments.

(1) Cancer incidence and mortality rates vary widely around the world. For the leading cancers in the U.S. and other developed countries – lung, colorectal, breast, and prostate – rates vary 10 times or more between those countries with the highest and those with the lowest rates [2]. In some areas, like Japan and Shanghai, China, rates of certain breast, colorectal, and other cancers have increased rapidly over a fairly short period of time [3]. Moreover, researchers have long observed that cancer incidence rates among migrants converge toward those of the

country of destination [4]. These ecologic observations suggest that something in lifestyle or environment (defined broadly) influences cancer. Diet is a likely candidate. It clearly varies among countries, has changed substantially in countries showing the rapid rate changes, and may change radically with migration and acculturation. The problem, however, is that other things – tobacco use, air pollution, physical activity, prevalence of color TV sets – vary along with diet. The international comparisons, time trend, and migration data are suggestive but hardly definitive when it comes to a causal link between diet and cancer.

(2) Tannenbaum carried out a number of experiments some five decades ago in which he demonstrated that total coloric as well as fat intake could modify mammary tumorigenesis in rodents [5]. Over the past few decades many researchers have shown that a variety of dietary factors can enhance or inhibit tumorigenesis in animal models, especially rodents administered potent chemical carcinogens. Although one can question the extent to which findings from such studies are generalizable to the human situation, the histologic and physiologic commonalities between cancer in rodents and humans are indisputable. The biologic fact remains that dietary change affects malignant processes in rodents that are not unlike those in people.

Diet and cancer hypotheses thus have credible scientific underpinnings as well as undeniable attractiveness from the perspective of prevention policy. It is hardly surprising that over the past two decades an enormous amount of both laboratory and epidemiologic resources have been invested in this area, and in recent years some reasonably consistent etiologic patterns have emerged. Nevertheless, the diet and cancer area remains fraught with controversy and contradictory data; the preventive implications of this large body of diet and cancer evidence are less than straightforward.

Research into dietary prevention of cancer has both biologic and social policy dimensions. The biologic questions deal with causal relations between dietary factors and cancer endpoints – does something we eat, or don't eat, influence the incidence of one or more cancers. These questions are asked without regard to whether a particular dietary modification – say, reducing meat or increasing vegetable intake – is feasible or practical. The issue is simply whether those changes work, whether they can inhibit carcinogenesis. Having established that a given dietary change reduces cancer incidence, one confronts a whole set of social policy questions bearing on how best to implement such a dietary modification on a population-wide basis. The social policy perspective may at times influence the biologic research program. If, for example, one concludes that it is too hard to get people to make substantial changes in what they eat, one might investigate 'simpler' manipulations such as the addition of supplements to the diet. There is a long history, though, of 'impractical' behavior change becoming the social norm. Some years back, for example, one could easily have questioned the feasibility of reducing fat intake from dairy products. Today, in the United States, many children have grown up concluding that anything other than skim or low-fat milk tastes too creamy. This paper focuses on the biologic questions, with no prior assumptions made about what dietary modification strategies are feasible and what ones are not.

What is diet?

Thus far we have been speaking of diet as if it were something comparable to benzene or aflatoxin exposure. What people eat, however, is extraordinarily complex, both in the range of ingested substances and the temporal variability (both long- and short-term) in intake. Many articles, both scientific and lay, extol the virtues or dangers associated with specific micro-nutrients, like beta-carotene, folate, or calcium, as well as various macro-nutrients like fat or fiber. Other articles focus on the salutary or deleterious consequences of consuming fruits and vegetables, red meat, fish, and so on. We have, then, these two different conceptual approaches to diet, which can be called in turn 'decompositional' and 'integrative'.

The decompositional perspective emphasizes the primacy of specific nutrients and other chemical constituents of food. The underlying premise, with

respect to cancer prevention, is that an individual chemical component has specific biologic activities influencing carcinogenesis and, further, that these biologic activities can be isolated from those associated with other components. This approach recalls the classical nutrient deficiency model of disease, according to which, for example, vitamin C intake below a given biologic threshold causes scurvy. The implicit assumption here is that we can successfully identify a chemical constituent's cancer-enhancing (or -inhibiting) activity, eliminate that constituent from (or add it to) the diet, and thereby ultimately reduce the incidence of malignancy.

The integrative perspective emphasizes whole foods or groups of foods, rather than individual food components. This conceptual approach derives from the fact that an individual's diet consists of many different foods, processed and prepared in myriad ways, and represents a highly complex mix of micro- and macro-nutrients, as well as other non-nutritive chemicals. The underlying premise here is that the biochemical and physiologic complexity resulting from the joint activity of these many substances does not lend itself readily, either theoretically or practically, to the isolation of single elements affecting carcinogenesis. It follows that the appropriate focus for cancer prevention research, and ultimately public health practice, is whole foods, food groups, or comprehensive food patterns (cuisines).

The practical consequences of these two conceptual approaches may differ radically. It is one thing to recommend that people double or triple their intake of fruits and vegetables, and quite another to suggest that everyone consume daily a pill containing micronutrients x or y, or some combination thereof.

Major hypotheses concerning relations between diet and cancer may be grouped primarily as decompositional or integrative.

Hypotheses based on nutrients and non-nutritive food constituents

Considerable attention has been given to a series of hypotheses concerning the influence of micronutrients, macronutrients, and non-nutritive chemical elements in foods on molecular and physiologic events important in carcinogenesis.

Anti-oxidant hypotheses

Reactive species, such as oxygen centered free radicals like superoxide and hydroxyl, have been hypothesized to cause cellular and possibly genomic damage in a variety of tissues [6]. It follows, therefore, that the redox potential of a cell may be critical in maintaining a balance between carcinogenesis and its prevention. Antioxidant substances with the capacity to scavenge or quench reactive species may thus have an anti-cancer effect. Micronutrients with antioxidant properties include carotenoids and vitamins A, C and E. Flavonoids and other non-nutritive constituents of fruits and vegetables (phytochemicals) also act as antioxidants. Specific examples of antioxidant hypotheses include beta-carotene and lung cancer [7], vitamin E in relation to prostate [8] and large bowel [9] cancers, and vitamin C and stomach cancer [10].

Other nutrient hypotheses

Other biologic actions relevant to carcinogenesis have been proposed for micronutrients. In addition to quenching reactive species, retinoids have been shown to influence cell proliferation and differentiation [6]. Intraluminal calcium may counteract the cytotoxic and potentially genotoxic activity of free bile and fatty acids and thereby modulate large bowel carcinogenesis [11]. Folic acid is involved in cellular methylation processes and DNA hypomethylation has been conjectured as an explanation for observed associations between folate and colorectal cancer [12].

Non-nutritive chemicals

Phytochemicals have generated considerable interest in recent years. Some of these, like flavonoids, are strong antioxidants [13]. Some phytochemicals have apparent hormonal activity and may protect against endocrine-associated tumors by competing with endogenous hormones for receptor space [14]. Given the many thousands of phytochemicals identified to date, many potential cancer-affecting actions (and interactions) are possible.

Macronutrients

Total dietary fat has long been hypothesized to influence breast, colorectal, and other major cancers [15]. This general hypothesis is complicated by the fact that specific types of dietary fat – linolenic acid in prostate cancer [16], for example – have been implicated in certain malignancies. Dietary fiber has been proposed to protect against large bowel carcinogenesis [17]. Again, research into this macronutrient has spawned subhypotheses about, for example, the effects of fermentable fiber [18] or nondigestible starch [19] on the internal milieu of the large bowel and thus on colorectal cancer.

Total energy intake

A number of researchers have proposed that total energy intake, rather than energy from specific macronutrients, is important in the etiology of cancer at various sites [20].

Food mutagens

Mutagenic and carcinogenic heterocyclic amines, produced by cooking meats at high temperatures, have been proposed as causal factors for cancer of the large bowel and other organs [21].

Alcohol

Alcohol is generally not considered a nutrient *per se*, but it does contribute to total energy intake and, for some people, may displace the intake of other macro- and micronutrients. Alcohol consumption has been implicated, with varying degrees of certainty, in the etiology of cancer at several anatomic sites [22].

Hypotheses based on individual foods, food groups, and food patterns (cuisines)

Because of the intimate and complex relation of nutrients (and non-nutritive constituents) to the foods in which they are contained, it can be difficult, on both biologic and statistical grounds, to isolate the cancer-affecting activity of micro- and macronutrients, phytochemicals, and so on. Moreover, dietary modification, other than simple micronutrient supplementation, generally involves multidimensional changes in intake. A person, for example, substantially reducing fat intake will often replace calories from fat with calories from carbohydrates, including vegetables, fruits, and legumes. A number of cancer researchers, therefore, have begun to focus more on specific whole foods, groups of foods, and patterns of intake (cuisines).

Foods

Because it is presumed that cancer-enhancing or -inhibiting activity is likely to be found in several foods with similar structural characteristics (the cruciferi, or red meat), investigators have tended to focus more on food groups. A few studies, though, have suggested anti-cancer activity for specific foods, such as garlic [23].

Food groups

Food group-cancer hypotheses include protection conferred by vegetable intake [24] or soy products [25] and increased risk stemming from red meat [26] consumption.

Dietary patterns (cuisines)

Just as the complex interactions of individual nutrients and other chemical constituents of food may be best captured by targeting the biologic actions of whole foods, so it may be argued that complex interactions among foods and food groups is best understood by focusing on broad dietary patterns. Thus vegetarian diets [27] have been proposed to reduce cancer risk, as have Mediterranean and Asian cuisines [28]. Large trials are currently examining whether an overall low fat/high fiber or grain/high vegetable and fruit eating plan, compared to the high fat, low fiber-grain, low vegetable and fruit pattern more typical of Western and developed countries, reduces the risk of colorectal and breast cancer [29].

Other nutrition-related factors

Obesity, a reflection of both dietary factors and physical activity, may have independent hormonal and other physiologic influences on carcinogenesis

[30]. Dietary modification may thus affect cancer risk directly, by altering the intake of foods or nutrients influencing carcinogenesis, or indirectly by changing adiposity and overall body composition. Physical activity affects total energy metabolism as well as body composition and, moreover, may have independent effects on physiologic processes relevant to cancer causation [31].

Testing dietary hypotheses

Diet and cancer hypotheses retain plausibility at multiple levels of biologic organization: the molecular, the physiologic, and the population. The problem is moving beyond plausible hypotheses to truly effective preventive strategies. Several types of research design are available for investigating diet and cancer relations.

Animal experiments

Animal experimenters can examine controlled diets, study cancer as an explicit endpoint, and integrate biomarkers in animal models, thereby establishing an exposure-intermediate endpoint-cancer continuum [32]. Moreover, whereas most animal studies have involved manipulation of individual dietary constituents (like % calories from fat), some investigators have begun to examine animal analogues of dietary patterns. Risio and colleagues, for example, showed that the rodent-version of a 'Western diet' diminished apoptosis and enhanced development of single-crypt dysplastic lesions [33]; this type of experiment could conceivably be extended in animals from intermediate markers to malignant tumors *per se*.

Extrapolating from rodent and other species models to the human context is always problematic, especially given the known anatomic and physiologic differences between laboratory animals and people. But again, pronounced effects, even in rodents, can be suggestive. Consistency in observed diet and cancer relations across species and tumor models makes it more likely that these relations hold in people. Moreover, elucidating physiologic, cellular, or molecular processes underlying tumorigenesis in animals can direct our research in humans. Animal studies, for example, that demonstrate dietary effects only on late-stage events suggest targeting human studies to relatively recent, rather than remote, diet.

Human metabolic (clinical nutrition) studies

Metabolic (or clinical nutrition) studies permit the investigator to examine the biologic consequences of manipulating diet in an explicit and quantifiable manner. The manipulation can involve administration of a supplement or wholesale alteration of macronutrients, foods, or food groups. Because the number of study participants is relatively small (in the dozens, rather than the hundreds or thousands characteristic of observational epidemiologic studies or clinical trials), 'biologic consequences' are generally non-cancer endpoints. Metabolic studies can examine, for example, the intake of high-carotenoid-containing foods or carotenoid supplements in relation to blood or tissue carotenoid levels [34]; induction of metabolizing enzyme systems by ingestion of cooked meat with high levels of heterocyclic aromatic amines [35]; the effect of fat or meat intake on blood hormone levels (androgens, estrogens, insulin, for example) [36]; the impact of a low-fat, high-fiber, high fruit and -vegetable eating plan on fecal bile acids [37] or short-chain fatty acids [38]; or the influence of ethanol consumption on endogenous estrogens, androgens, and other hormones in women [39].

The advantages of metabolic studies are several. First, they can help refine dietary assessment questionnaires as well as the databases associated with these instruments. An example are recent studies of the types and amounts of mutagenic substances produced by high-temperature cooking of various meats [35]. Second, such studies can further the development of biologic markers of dietary intake by evaluating the relation of blood or tissue nutrient levels to intake [40]. Third, one can examine the biologic effects of intervening with well-characterized diets. Finally, because these studies involve a range of molecular, biochemical, physiologic, and

histologic biomarkers as endpoints, valuable insight may be gained into the microprocesses underlying carcinogenesis.

This last strength, however, embodies at the same time the major limitation of metabolic studies: the relation of noncancer endpoints to cancer is not sufficiently clear to warrant definitive conclusions about diet and malignant disease from these investigations. Studies demonstrating that dietary fat or fiber modulate rectal mucosal proliferation [41] suggest that these nutritional factors play a role in colorectal carcinogenesis. Such studies, however, are not conclusive. Data establishing a direct and necessary link between colorectal mucosal hyperproliferation and cancer are sparse at best; whether all or only some colorectal malignancies are preceded by hyperproliferation is unknown. Even if colorectal cancer risk is markedly increased in people with hyperproliferative large bowel epithelium, it is possible that the nutritional factors under consideration influence some other biologic intermediates that inhibit carcinogenesis [42]. In other words, studies of diet and noncancer endpoints (and least those that are not necessary cancer precursors) have the potential to give us the wrong answer about diet and cancer *per se*.

Observational studies

Because of the inferential limitations inherent in both laboratory and metabolic studies, researchers put a great deal of stock in human population studies with explicit cancer or neoplastic endpoints.

Whether an observational epidemiologic study begins by identifying cancer cases and a set of appropriate controls (case-control design) or delineating a cancer-free population that eventually yields cancer cases (and a great many more non-cases) from the original group (cohort design), this type of investigation does involve explicit cancer endpoints in humans [43]. This type of study thus avoids the problems inherent in extrapolating to human malignancy from animal tumors or surrogate endpoint markers like proliferation or hormones. A second advantage of observational epidemiologic studies is the possibility of examining exposures of long duration, that is, dietary intake over many years. Third, large epidemiologic studies, and they have to be quite large for this purpose, permit the evaluation of interactions between dietary and other risk factors. This can be particularly valuable in situations where another risk factor like obesity tends to overwhelm and obscure the association with a weaker, but still important, dietary factor. Analyses of diet and malignancy among thin women, for example, might therefore be especially revealing. Lastly, investigators now have the opportunity to integrate intermediate markers of carcinogenesis into large-scale observational epidemiologic studies, which allows evaluation of the joint relations among dietary factors, markers, and cancer. Several ongoing cohort studies of diet and cancer [44, 45] have obtained blood specimens on participants, enabling analyses of relations between, say, dietary fat or alcohol, estrogen levels, and breast cancer.

Observational studies also have their limitations, though, as discussed in the following sections.

Lack of dietary heterogeneity

In general the investigator requires a reasonable range of exposure in order to make useful biologic comparisons. If one were to conduct a study in a population consisting only of 2 pack-a-day smokers, one would be hard pressed to show any smoking-lung cancer link because there would be no non- or lighter-smoking individuals for comparison. The same type of problem arises in nutritional epidemiology: in a specific geographic region, for a particular nutrient or food, people often tend to eat somewhat alike. This lack of dietary heterogeneity may make it difficult to make useful comparisons between high and low levels of nutrients and foods. Researchers have recently adopted some innovative approaches to dealing with this problem. These include the study of multiple ethnic groups [46] and countries [44] and the implementation of a two-phase sampling design that explicitly captures the extremes of intake distribution [47].

Dietary measurement error

The 'exposure' in nutritional epidemiology is extraordinarily complex. Not only must the researcher worry about what foods are eaten, in what

amount and how often, but food processing and preparation may also figure into the diet-cancer equation. Because of this complexity, and the imperfection in human recall, the assessment of diet is subject to considerable error. As a general rule, this error tends to attenuate the magnitude of association between a given dietary factor and cancer [48]. That is, a true relative risk of 2 (representing a doubling of risk) for those in the highest, compared to the lowest, category of a given nutrient or food, might, in the context of dietary measurement error, be observed as a relative risk of only 1.4. The sample size required to detect a relative risk of 1.4 is considerably greater than that required to detect a relative risk of 2.0.

A number of statistical methods have been developed for estimating and adjusting for dietary misclassification [49], but these methods make restrictive mathematical assumptions or are otherwise not universally accepted [50]. The calibration (validation) studies required for the statistical corrections – involving the administration of a second, more labor intensive assessment instrument, such as a series of 24-hour dietary recalls, to a subset of those responding to the primary instrument, usually a food frequency questionnaire – can be very expensive. Furthermore, energy adjustment procedures remain controversial. It may not be possible, for example, to separate specific effects of fat on cancer from those of total caloric intake, though it may be possible to generate overall dietary recommendations [51].

Work continues on refining our techniques for assessing diet, including updating the associated data bases with new information on standard nutrients as well as developing new data bases for such constituents as heterocyclic amines [35] and various phytochemicals [13]. Efforts are also under way to apply findings from cognitive psychology to questionnaire design [52]. New approaches are being explored for analyzing combinations of nutrients and foods in dietary data, though, at present, there is no standardized, readily interpretable method for identifying dietary patterns. Nevertheless, it is unclear how much better we can improve our dietary assessment instruments. For that reason researchers remain very interested in developing biomarkers of intake. Although blood levels are reasonable reflections of intake of some specific nutrients, clear-cut, objective markers for consumption of some key macronutrients and foods are not yet available. There is, for instance, no clear-cut 'objective' marker of individual dietary fat. Measuring blood carotenoids, however, gives some idea of consumption of carotenoid-rich fruits and vegetables and is of some value in assessing total fruit and vegetable intake [53]. This is an active area of research [54].

Recall and selection bias

Case-control studies may suffer from both recall and selection bias [43]. Recall bias results if, for example, those diagnosed with cancer tend to over- or underreport their intake of certain foods or nutrients. Several investigators have recently attempted to evaluate the extent of recall bias in case-control studies of diet and cancer by assessing diet both before and after diagnosis in persons enrolled in an ongoing cohort study [55, 56].

Selection bias may arise if control participation is somehow associated with the exposure of interest. Because a number of factors, some of which may be associated with the exposure, influence participation in studies, a large non-participation rate makes slection bias a definite concern. To reduce the possibility of this bias, epidemiologists have tried innovative approaches to increasing participation rates in case-control studies. It is unlikely, though, that these efforts will completely eliminate the possibility of biased results in case-control studies, especially given the fact that relative risks in the area of diet and cancer are likely to be modest in the first place. In other words, it will be difficult to preclude the possibility that a 50% increase in risk (a RR of 1.5) is simply due to some combination of recall and selection bias. Nevertheless, the case-control design has value for investigating emerging hypotheses in a comparatively short time as well as studying relatively rare malignancies lying beyond the statistical power of most cohort studies.

Prospective cohort studies of diet and cancer generally avoid recall and selection biases and have therefore, despite their cost and logistical demands, come into increasing favor in recent years. Several

large studies of this type have now been initiated around the world.

Confounding

Confounding bias arises if people who eat differently also differ in other ways related to the genesis of cancer. Confounding remains a serious potential problem for all observational studies, cohort as well as case-control. Although there are a variety of techniques for measuring and adjusting for potential confounding factors, it may not always be possible to capture these factors in interviews and questionnaires. If the magnitude of association between an exposure and cancer is very high, this is unlikely to be explained by confounding. (For relative risks in the neighborhood of 10–20, as for smoking and lung cancer, one would have to posit that exposure to some lung carcinogen other than tobacco smoke was 10 to 20 times more common in smokers than nonsmokers.) If the relative risk is modest, as it likely is in diet and cancer relations, confounding remains a nagging concern.

Timing of the relevant dietary exposure

Most nutritional epidemiologic studies of cancer assess recent diet. Food frequency questionnaires generally ask what the study participant typically ate in the previous year. This is a reasonable approach if diet affects late-stage carcinogenesis or is a fairly accurate proxy for cumulative lifetime exposure. It is plausible, however, that early life diet – specific nutrients, foods, or even total energy intake – may be important in modulating subsequent cancer risk [57]. Methodologic work is establishing whether early diet can be assessed with any useful degree of accuracy [58]. One research group is attempting to create a cohort of very young women (daughters of the participants in the Nurses Health Study [45]), which will assess diet directly and thereby avoid the error resulting from remote diet assessment.

Intervention studies

Randomized controlled trials, long important in evaluating the efficacy of therapeutic interventions, have assumed an increasingly important role in diet and cancer research. The diet-related interventions adopted in such trials may be one of two types: supplements, such as vitamin pills or fiber wafers, or more comprehensive eating plan modifications involving changes in one or more macronutrients or foods.

Perhaps the predominant rationale for conducting these complex and expensive studies is the higher level of inferential certainty conferred by trial results. In particular, because participants are assigned randomly to the study arms, biological and demographic characteristics of the two groups are very likely to be similar, especially if the sample size is reasonably large. What this means is that the possibility of confounding, whereby the intervention participants differ from those in the control arm on some other characteristic causally related to the development of cancer, is greatly minimized.

Furthermore, heterogeneity of dietary intake, often difficult to achieve in an observational epidemiologic context, is generally an inherent feature of trial design. The multi-center Polyp Prevention Trial (PPT), sponsored by the National Cancer Institute, investigates the effect on large bowel adenoma recurrence of a low fat, high fiber, high fruit and vegetable eating plan [29]. The usual intake among middle-aged and older persons in this country, as reflected in the PPT control group, is about 35% calories from fat, 8 to 10 grams of dietary fiber per 1000 kcal, and about three daily servings of fruits and vegetables. The goals for the intervention group in this trial are 20% calories from fat, 18 g of fiber per 1000 kcal/day, and five to eight servings of fruits and vegetables daily. This represents a substantial variation in intake along several dietary dimensions; it is difficult to capture the same intake difference among participants in a standard observational epidemiologic study conducted in this country.

Trials also have limitations, though, and cannot completely supplant other research designs. First, an intervention is generally of relatively short duration and the effects of much longer exposure cannot be easily tested in a trial. Consumption over many decades may well be most relevant. Second, the intervention is generally fixed for the duration of the

trial. This can be problematic given the initial uncertainty in selecting the proper dosage or administration interval for a supplement study or the exact components of an eating plan in a dietary intervention. It can be especially frustrating to initiate a large-scale trial and realize, with the emergence of new evidence after two or three years on-study, that it would have been desirable to test a different micronutrient, or the same substance at a different dose.

Third, dietary interventions, as opposed to supplements, cannot be double blind. If participants know they are altering their usual intake, they could also be changing other things related to cancer simply as a consequence of being in the intervention arm. Fourth, most interventions are carried out only in adults. It would be difficult in a trial to test the hypothesis that early-life diet influences carcinogenesis, given the long latency period for malignant disease. Fifth, it can be formidable to guarantee participant adherence over many years. Finally, trials are relatively labor-intensive undertakings and consume a large quantity of research resources in a tightening fiscal environment.

The factorial design, which provides essentially two or more studies for the price of one, is likely to become a common feature of future diet and cancer trials [59]. Trials may also use cancer precursors like adenomatous polyps as endpoints, although inferences from such noncancer marker studies are more limited than those from studies with explicit cancer outcomes [60]. Future intervention studies would clearly benefit from the continued development of biological intake markers, as well as innovative strategies for enhancing dietary adherence. Several researchers have recently emphasized a need for longer follow-up in nutritional supplement and dietary trials [61].

Intervention studies of diet and cancer are really in their infancy. These studies clearly have their theoretical and logistical limitations, but well-conducted trials have the potential to make qualitative advances in our understanding of diet-cancer questions. Strong, unambiguous results from a supplement or dietary trial would be very compelling.

Diet and genes

It is hardly surprising that the explosion of work in the molecular genetics of cancer should intersect research in dietary etiology and prevention. A natural question for animal researchers is whether diet can modulate tumorigenesis in gene-knockout models. In that vein, Hursting et al. have recently shown that caloric restriction reduces tumor burden in p53-knockout transgenic mice [62].

Whether this type of finding is applicable to people carrying 'major' cancer genes is unknown, but the demonstration of joint gene-diet activity in rodents at least suggests that such interaction has biologic reality and merits exploration in humans. One can envision, for example, that dietary change could modulate the neoplastic process in young people carrying the gene for familial polyposis – much the same way that a low phenylalanine diet minimizes the adverse sequelae of phenylketonuria [63].

Considerable interest has been kindled by what have become known as 'susceptibility' genes, especially polymorphic metabolizing genes involved in the activation or detoxification of xenobiotics and dietary factors. The basic paradigm here is that an 'interaction' between dietary factors and one's genetically determined metabolic status influences cancer risk at various anatomic sites. In other words, the relative risk for a given nutrient or food will be higher among those with the susceptibility-conferring allele than those without it. Thus, researchers have reported increased colorectal cancer, in relation to ingestion of red, well-done, browned, and barbecued meat (likely to contain more mutagenic-carcinogenic heterocyclic amines) among those who are rapid metabolizers by the N-acetyl transferase (NAT2) and cytochrome P4501A2 (CYP1A2) pathways [64]. Glutathione S-transferase M1 (GSTM1) status has been suggested to modify the association between phytochemical intake and cancer [65]. The relation of folate intake to colorectal cancer may be altered in individuals homozygous or heterozygous mutant for the methylenetetrahydrofolate reductase (MTHFR) gene that codes for an enzyme critical in folate metabolism and methyl group availability [66]. Vitamin D

receptor polymorphisms have been associated with prostate cancer risk [67].

We are likely to see many more reports of such gene-diet interactions. This is an interesting area of research but it does present both theoretical and logistical problems. To the extent that genotype strongly predicts phenotype, one can be fairly confident in confining analyses to genotypic variants. In a number of cases, though, xenobiotic metabolism is not wholly genetically determined but instead can be induced by dietary factors [35]. Furthermore, more than one gene (each with multiple allelic variants) may be involved in metabolism of a dietary factor, and a given gene may have more than one function (pleimorphism). Thus, we may be able to capture the integrated biochemical complexity inherent in certain pathways only by directly assaying metabolic phenotype. Phenotypic assays, however, tend to be more difficult and expensive to carry out than DNA analyses [68].

Some 20 susceptibility genes have been identified so far; it is entirely possible that dozens more will become known in future years. When we look at many dietary factors in relation to polymorphisms in many genes, we will find some 'positive' results by chance alone. Unfortunately, given the rapid expansion of basic molecular and cellular knowledge, having prior biologic hypotheses will no longer be of much help in sorting through these myriad diet-gene associations. For example, one might expect individuals null for an enzyme that detoxifies carcinogens to be at increased cancer risk. One could, however, explain such individuals being at *lower* risk on the grounds that certain cancer-protective compounds in foods are not being cleared. Because some diet-gene associations will crop up by chance, and because it appears to be possible to come up with some biologic rationale for even diametrically opposite findings, replication of research results in this field is critical.

A further statistical issue merits consideration. Suppose one finds that the relative risk for a dietary factor Z is elevated among a given genetic subgroup. One would certainly treat this finding cautiously if it turned out that Z showed no overall relation to cancer and the test for interaction between Z and metabolic gene status were not statistically significant. Researchers need to be careful to design studies with sufficient power to permit statistical tests of interaction – and to report the results of the interaction analyses. An intrinsic difficulty here is that the sample size required to detect interactions is considerably greater than that needed to detect main effects [69].

Finally, this line of research is rather problematic from a prevention perspective. Given the biologic complexity involved in the metabolism of foods and nutrients, will we ever be comfortable in designating some individuals as 'non-susceptible'? If a series of reports should indicate that eating heterocyclic amine-laden well-done red meat increases colorectal cancer risk only among rapid acetylators, would it be responsible to tell slow acetylators that they can eat all the barbecued steak they want and not worry about cancer in their large intestine? Probably not, illustrating the complexity in formulating practical dietary strategies in the context of this new research.

Preventing major cancers: Is dietary change a realistic strategy?

This paper has dealt primarily with general theoretical and practical problems affecting our understanding of how dietary change might prevent malignancy. The focus has thus far been on the diet side of the diet-cancer story and the strengths and limitations of the various scientific study designs used in this field. This section starts from the cancer side and assesses what we know about the extent to which diet can prevent four major malignancies: lung, breast, colorectal, and prostate. A recent site-by-site review of nutrition and cancer is available elsewhere [70].

Lung cancer

Tobacco smoking is indisputably the major (though not the only) cause of the world-wide lung cancer epidemic. There is now good evidence that avoiding exposure to tobacco smoke reduces the incidence of the disease [71]. For many years, however, re-

searchers have wondered whether the intake of anti-oxidant carotenoids, beta-carotene in particular, influences lung carcinogenesis [1]. The argument is made that, whereas avoiding smoking is the primary means to prevent lung cancer, carotenoid supplementation might benefit those who cannot stop smoking or those who have stopped but remain at increased risk because of many years of prior exposure. A very large body of observational epidemiologic data, based on self-reported intake as well as blood level assessment, has suggested that lung cancer risk is inversely related to intake of beta carotene/carotenoids or fruits and vegetables [72]. In contrast, recently published results from three clinical trials – conducted among Finnish smokers [73], asbestos workers and smokers [74], and U.S. physicians [75] – indicate no protective effect of beta-carotene on lung cancer incidence. This is an instance where results from large, well-designed clinical trials raise questions about fairly consistent findings from observational studies. One possible explanation for the disparity between intervention and observational findings is that beta-carotene is simply a proxy for other nutrients (including other carotenoids) and phytochemicals found in fruits and vegetables. The observational evidence is consistent with the notion that enhanced consumption of fruits and vegetables could reduce lung cancer risk, even among smokers, but this is not proved. Eating more fruits and vegetables could provide protection against lung cancer caused by other exposures such as radiation, cooking smoke, and so on, but again this has not been tested systematically. Thus, diet may help a little, it probably doesn't hurt, but the key to preventing lung cancer is avoiding smoking and the other known causes of lung cancer.

Breast cancer

Breast cancer remains a frustrating disease for those interested in prevention. Whether and how diet influences the hormone-breast cancer connection [76] – or whether diet affects mammary carcinogenesis independent of any endocrine processes – has long been the subject of conjecture and research [77]. The many animal experiments certainly lend biological credence to a diet-breast cancer link. Dietary differences could explain the international variation in incidence rates. But the observational epidemiologic evidence has shown few if any links between diet and breast cancer. In particular, the dietary fat-breast cancer hypothesis is largely unsupported by the evidence from cohort studies, which are unlikely to be marred by recall or selection bias [78]. It has been recently suggested that such epidemiologic studies suffer from a systematic bias, whereby overweight women tend to underreport their fat intake, which would attenuate a true relative risk reflecting the international rate variation (a RR of about 1.5) down to the 1.0–1.1 seen in the prospective studies [79]. This statistical suggestion is currently being evaluated. Dietary homogeneity is another possible weakness in the observational epidemiologic literature on diet and breast cancer; further insight might emerge from observational studies explicitly introducing greater intake variability, such as the EPIC study [46] and the NIH-AARP Health Study [47]. The hypothesis has emerged that higher energy intake and growth rate in early life might affect breast carcinogenesis, but this relation may be difficult to nail down [77].

There is also a major intervention study of the diet-breast cancer question. The Women's Health Initiative (WHI), a very large, ambitious NIH-sponsored study of heart disease, cancer, and osteoporosis among women in the United States, will randomize 63,000 postmenopausal women aged 50 to 79 in its controlled clinical trial component [80]. The trial has three interventions, although women can choose to be randomized into two or three of the overlapping studies. The interventions include a low-fat eating plan (with explicit emphasis on increasing consumption of fruits and vegetables), hormone replacement therapy, and calcium/vitamin D supplementation. 48,000 women will be randomized into the dietary component of the study (19,200 in the intervention arm, 28,800 in the control arm). The trial will require four years for protocol development and nine years of follow-up. A successful WHI will likely lend a new and important dimension to the evidence on diet and breast cancer.

In light of the extensive data implicating reproductive hormones in breast carcinogenesis, further metabolic studies of the effects of foods and nutrients on estrogens and androgens (and possibly insulin) will be valuable, especially when considered in conjunction with new (and larger) studies of the precise relations of hormones and breast cancer.

A number of studies suggest that obesity increases breast cancer risk, especially in postmenopausal women [30]. Adult weight gain, in particular, may enhance risk, suggesting that weight maintenance, or possibly weight loss, could reduce a woman's chance of developing this disease [81]. A few studies also suggest that obesity reduces survival from breast cancer [82]. Obesity, of course, is a product of total energy intake, physical activity, and genetic factors acting jointly over many years. To the extent, then, that avoiding weight gain and obesity truly reduces breast cancer incidence and mortality, diet may be said to have a role in prevention.

In general, though, the possibility of preventing breast cancer through dietary change remains speculative – and contentious.

Prostate cancer

Prostate cancer etiology remains elusive. Some very interesting findings have emerged, largely from observational studies, suggesting that red meat and animal fat may increase prostate cancer risk and that vitamin E or vitamin A may be protective [83]. More observational epidemiology is needed to confirm these findings. Metabolic studies of, for example, red-meat and fat in relation to androgens may provide additional biologic support for this hypothesis. It may be time in the near future to go to trials to further test these hypotheses. Research into dietary prevention of this malignancy is in its early stages.

Colorectal cancer

There is an inherent biologic plausibility to the notion that diet should affect epithelial carcinogenesis in the gastrointestinal tract, and among the major malignancies colorectal cancer arguably offers the greatest promise for dietary prevention.

A great deal of ecologic, laboratory, and clinical nutrition data support a connection between diet and colorectal cancer. Numerous observational epidemiologic studies suggest that colorectal cancer risk is altered by intake of fat, red (and possibly cooked) meat, fiber, resistant (nondigestible) starch, fruits and vegetables, folate, and other dietary factors [84, 85]. Not all the evidence is consistent, though. Some epidemiologic studies do not show the fat, meat, and fiber associations that have been observed in other investigations [85]. Nevertheless, an attractive integrative hypothesis, involving macronutrients and foods, emerges: a dietary pattern with low intake of fat and red meat and high consumption of fruits, vegetables, grains and legumes lowers colorectal cancer risk.

Micronutrients have also been linked to large bowel malignancy. A number of recent reports suggests an inverse relation with dietary folate [86], but it is unclear whether folate influences large bowel carcinogenesis independently or is merely a reflection of fruit and vegetable intake. Intake of calcium, which is thought to neutralize intra-luminal fatty and bile acids, has also been linked inversely to colorectal cancer, although a recent meta-analysis suggests that this effect, if any, is likely to be small [87].

The diet-colorectal cancer story is one where concordant findings from intervention studies would constitute a qualitative advance in the prospects for dietary prevention of this disease. Several adenomatous polyp recurrence trials have been completed or are now under way around the world. These include trials of vitamin supplements [88]; calcium [89] (and Baron J, personal communication); fiber supplements [89, 90]; folic acid (in a factorial design with aspirin) (Baron J, personal communication); fat, fiber and beta-carotene [91]; and a low-fat, high-fiber, high-fruit and vegetable eating plan in the PPT [29]. The biologic rationale for such trials is the increasingly verified notion of the adenoma-carcinoma sequence: most large bowel cancers develop from adenomas. Polyp trials are attrac-

tive because the high annual recurrence rate – 10% or more (approximately two orders of magnitude greater than the incidence rate for colorectal cancer) – means that such a study can be carried out on a much smaller, faster, and cheaper scale than an intervention study with cancer as the endpoint [92]. In spite of some theoretical limitations in generalizing from adenoma findings to cancer, these polyp trials, if large enough [93], have the potential to yield quite compelling evidence.

Two new large trials have large bowel cancer as an explicit endpoint. The Women's Health Study will examine the effect of β-carotene (50 mg qod), vitamin E (600 IU qod), and aspirin among some 40,000 postmenopausal female health professionals 45 years of age and older (Buring J, personal communication). This study employs a 2^3 factorial design and evaluates the three factors in relation to cardiovascular endpoints as well as total cancer and cancers of the breast, lung, and colon. The Women's Health Initiative (WHI) will also provide data on colorectal cancer, having approximately 90% power to detect a reduction of approximately 25% in the incidence of this malignancy.

The prospects for preventing colorectal cancer hinge in part on the results of these trials. An unambiguous, positive result from the PPT, for example, taken in conjunction with findings from observational epidemiologic studies, would provide a solid foundation for public health recommendations for a low fat/low meat, high fruit/vegetable/grain dietary pattern. A confirmatory finding from the WHI would make the foundation that much stronger.

Conclusion

Willett, in a recent update of the Doll and Hill estimates, concludes that dietary change could eliminate a little over a third of incident cancer in the United States. His boundaries around this prevention estimate are somewhat narrower (20–42%) than those of Doll and Hill, reflecting more than a decade of additional research, but even this narrower range acknowledges considerable uncertainty.

It makes biologic sense that diet should profoundly influence malignant disease. Certainly the diet-cancer connection is attractive from a practical, public health perspective. We have a ways to go, though, before we can elevate dietary recommendations and prevention strategies to the same scientific level as those now promulgated for tobacco smoke and radiation. But the prospect of preventing anything near one-third of human malignancies is more than enough to warrant continued, intensive efforts in this difficult area of diet and cancer.

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